4160-01

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

[DOCKET NO. 83N-0070]

LICENSING OF A BIOLOGICAL MONOCLONAL ANTIBODY PRODUCT PREPARED BY HYBRIDOMA TECHNOLOGY

48 FR 50795
11-3-83

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that any biological monoclonal antibody product prepared by hybridoma technology that is intended for in vivo use or for in vitro testing of a licensed biological product is a biological product, subject to licensure under the Public Health Service Act. In those instances where a licensed manufacturer of a final product intends to obtain partially processed monoclonal antibody from another establishment, that second establishment and its partially processed antibody also must be licensed.

83-210

83N-0070

N1

FOR FURTHER INFORMATION CONTACT:

For general information:

Albert Rothschild,

National Center for Drugs and Biologics (HFN-813),

Food and Drug Administration,

8800 Rockville Pike,

Bethesda, MD 20205,

301-443-1306.

For licensing information:

Donald Hill,

National Center for Drugs and Biologics (HFN-825),

Food and Drug Administration,

8800 Rockville Pike,

Bethesda, MD 20205,

301-443-5433.

SUPPLEMENTARY INFORMATION: A monoclonal antibody product prepared by hybridoma technology consists of homogeneous immunoglobulins all of which have identical structure and identical antibody reactivity. Hybridoma technology used in manufacturing monoclonal antibodies involves fusing a normal antibody-forming cell with a malignant cell (e.g., a myeloma cell) to create a continuously growing clone of hybrid antibody secreting cells, the hybridoma. Selected hybrid cells are then cloned and propagated in the peritoneum of an animal (mouse) or in tissue culture where

quantities of the epitope-specific monoclonal antibody are produced. Usually, the monoclonal antibody is separated from the ascitic fluid of the animal or the tissue culture medium, purified, and prepared for use as a final product.

Monoclonal antibodies are highly specific and homogeneous and are, therefore, potentially valuable in the manufacture of a variety of in vivo products, e.g., tissue specific antibody labeled with a radioisotope or a drug, or neutralizing antibody to a drug, toxin, or microbe. Monoclonal antibodies also are used as the active components of in vitro diagnostic products, e.g., a blood banking reagent intended for the testing of a licensed biological product.

FDA is issuing this notice to advise interested persons of the licensing requirements for a monoclonal antibody product prepared by hybridoma technology that is intended either for in vivo use or for in vitro testing of a licensed biological product. Section 351(a) of the Public Health Service Act (42 U.S.C. 262(a)) requires, in part, that any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, applicable to the prevention, treatment, or cure of diseases or injuries of humans must be propagated or manufactured and prepared at an establishment holding an unsuspended and unrevoked license. A monoclonal antibody product is analogous to both an antitoxin and a therapeutic serum. Therefore, by definition,

any monoclonal antibody product intended either for in vivo use or for in vitro testing of a licensed biological product is a biological product and is subject to the licensing provisions of the Public Health Service Act. Accordingly, after the initial development of a hybridoma cell line, any manufacturing process for the preparation of a monoclonal antibody product intended either for in vivo use in humans or for in vitro testing of a licensed biological product, must be performed at an establishment holding an approved license to manufacture the product. In those instances where the licensed manufacturer of the final product intends to obtain partially processed monoclonal antibody from another establishment, that second establishment and its partially processed monoclonal antibody also must be licensed. To ensure that a partially processed monoclonal antibody product is not misbranded, the label affixed to each container of such a product intended for further manufacturing into injectable products must contain the statement "Caution: For Manufacturing Use Only"; and the label for such a product intended for further manufacturing into noninjectable products must contain the statement "Caution: For Use in Manufacturing Noninjectable Products Only". Manufacturers seeking licensure of a monoclonal antibody product must file license applications with the Office of Biologics, Licensing Branch (address above). The license application for either a partially processed or final monoclonal antibody product must

include, among other information, the manufacturing methods, specifications, and controls that ensure the safety, purity, potency, and effectiveness of the final product. An in vivo monoclonal antibody product that is intended to be administered to humans presents a greater potential risk to health than an in vitro monoclonal antibody product that is not intended to be administered to humans. Accordingly, FDA's requirements may be more stringent for license approval for partially processed or final monoclonal antibody products intended for in vivo use than FDA's requirements for license approval for partially processed or final products intended for in vitro use. A monoclonal antibody product intended for use in vivo or in vitro that is undergoing development before marketing may be shipped in interstate commerce under the provisions of §§ 312.1(g) or 312.9 (21 CFR 312.1(g) or 312.9), respectively.

If a licensed or unlicensed manufacturer of a partially processed or final monoclonal antibody product that is intended for use in vitro intends to market the product for use in vivo, FDA emphasizes that before marketing the monoclonal antibody product that is intended for use in vivo, the manufacturer must file with FDA a new license application for the partially processed bulk or final monoclonal antibody product.

Dated: October 26, 1983.

OCT 26 1983

Mark Novitch

Mark Novitch
Acting Commissioner of
Food and Drugs

CERTIFIED TO BE A TRUE COPY OF THE ORIGINAL